

Department of Chemistry, University of Utah

**3- $\beta$ -D-Arabinofuranosyladenine (I)**

K. R. Darnall and Leroy B. Townsend

9- $\beta$ -D-Arabinofuranosyladenine has been found to inhibit the growth of several tumors (2,3) and to be incorporated into the acid soluble nucleotides and RNA of liver in the mouse (3). Recently 9- $\beta$ -D-arabinofuranosyladenine has been found (4) to act as a non-competitive inhibitor of DNA polymerase in TA3 cells. The synthesis of 9- $\beta$ -D-arabinofuranosyladenine has been reported (5) to occur from the reaction of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride with N<sup>6</sup>-benzoyladenine in methylene chloride. During a large scale run of 9- $\beta$ -D-arabinofuranosyladenine prepared by this procedure (6), a substantial quantity of a second nucleoside described by Glaudemans and Fletcher (5) as probably "9- $\alpha$ -D-arabinofuranosyladenine" was obtained from the filtrate. It has been noted (5) that a polar solvent (dimethyl sulfoxide) greatly increased the yield of this " $\alpha$ -anomer". Since the  $\alpha$ -anomer of 6-thioguanosine has shown definite carcinostatic effect it seemed of interest to isolate and fully characterize the  $\alpha$ -anomer of 9-D-arabinofuranosyladenine. The crude 9- $\beta$ -D-arabinofuranosyladenine obtained was recrystallized from 2-propanol as described (5). Concentration of the 2-propanol filtrate gave another nucleoside derivative which was subsequently purified by fractional crystallization from ethyl acetate to yield a product (I), m.p. 161-163°. This product (I) gave a correct elemental analysis for a 9-(2',3',5'-tri-*O*-benzyl-D-arabinofuranosyl)adenine, the assumed " $\alpha$ -anomer", discussed by Glaudemans and Fletcher (5). Debenzylation of I was accomplished with 10% palladium on carbon in aqueous ethanol at 65° to give a crystalline D-arabinofuranosyl nucleoside of adenine (II), m.p. 233-234°. Inspection of the ultra-violet absorption spectrum of II (see Table I) readily revealed that II was not a 9-substituted adenine derivative. Unequivocal assignment of N-3 as the site of glycosidation was made utilizing procedures previously outlined (7) for adenine nucleoside derivatives. Application of the  $\Delta \lambda$  min. rule gave a  $-7.5 \mu$  value which indicated N-3 as the site of glycosidation. Further substantiation of this assignment was provided by a  $pK_a$  of 5.32 which compares favorably with that of 3- $\beta$ -D-ribofuranosyladenine (8) ( $pK_a$  5.5).

Conclusive and final confirmation of attachment of the sugar moiety at N-3 was obtained from the p.m.r. spectra since the  $\Delta \delta$  rule (7) gave a 40 c.p.s. value for II (Fig. 2) and 6 c.p.s. value for 9- $\beta$ -D-arabinofuranosyladenine (Fig. 1).

It is of interest that the large  $\Delta \delta$  observed for II (Fig. 2) appears to be the direct result of deshielding

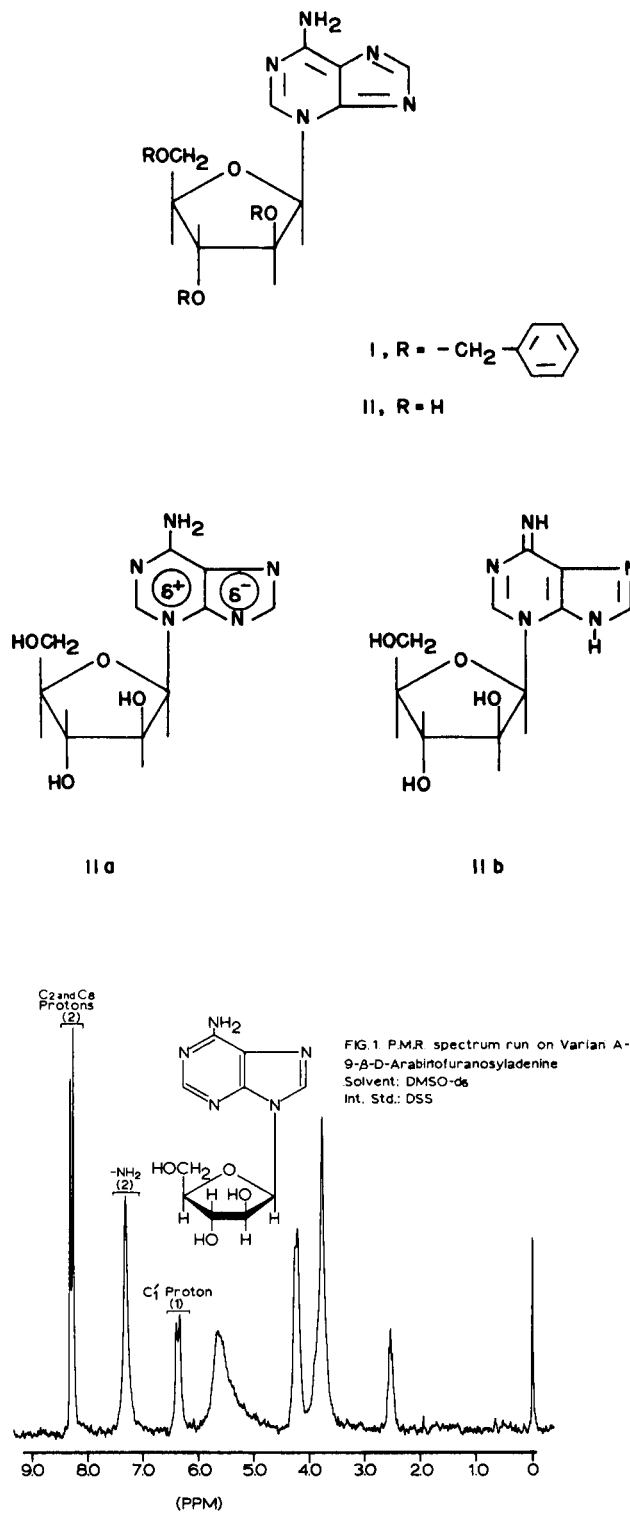


TABLE I

Adenine	$\lambda$ max	$\lambda$ min	$\Delta \lambda$ min = $\lambda$ min (pH 1) - $\lambda$ min (H <sub>2</sub> O or MeOH)	$\Delta \delta$ = c.p.s. diff. between 2 and 8 protons
1-Methyl- (14)	pH 1	258		
	MeOH	270	228.5	26
	pH 11	270	244	
3-Methyl- (15)	pH 1	272.5		
	MeOH	273	244.5	28
	pH 14	272	243	
				- 9.5
7-Methyl- (16)	pH 1	271.5	236	
	MeOH	267-273	230.5	6
	pH 14	266-271	231	
				+ 5.5
9-Methyl- (17)	pH 1	258.5	230	
	MeOH	261	225	3
	pH 11	260	226.5	
				+ 5.0
9-( $\beta$ -D-ribofuranosyl)-	pH 1	256	230	
	MeOH	258	225	
	pH 11	258	224	12
3-( $\beta$ -D-ribofuranosyl)- (18)	H <sub>2</sub> O, 0.1 N HCl	275	237	
	H <sub>2</sub> O, pH 7	277	245	48
	H <sub>2</sub> O, 0.1 N NaOH	278	247	
				- 8.0
9-( $\beta$ -D-arabinofuranosyl)-	pH 1	257.5	230	
	EtOH	258	225	6
	pH 11	259	226	
3-( $\beta$ -D-arabinofuranosyl)- (II)	pH 1	275	237.5	
	H <sub>2</sub> O	275	245	42
	pH 11	275	245	
				- 7.5

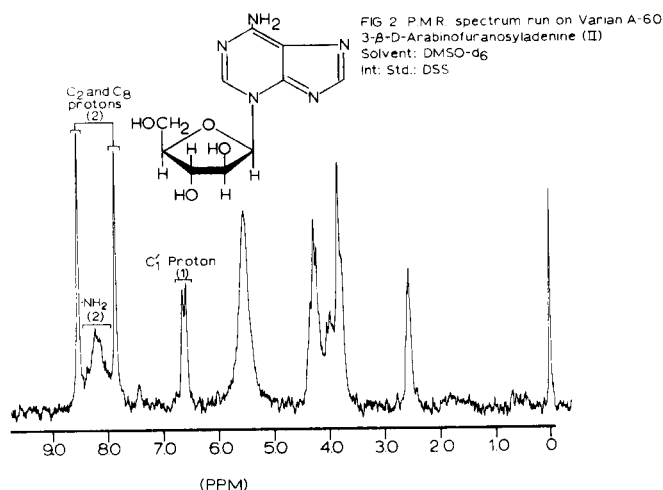


FIG 2 PMR spectrum run on Varian A-60  
3-β-D-Arabinofuranosyladenine (II)  
Solvent: DMSO-d<sub>6</sub>  
Int. Std.: DSS

one aromatic proton while shielding the other (presumably the 2 and 8 respectively). This indicates that a charged species (9) such as IIa probably contributes more to the over-all structure than II or IIb in DMSO-d<sub>6</sub>. In fact, structure IIb (the "imino" form) can be excluded since from a visual inspection of the p.m.r. spectrum of II (Fig. 2) there is observed an absorption peak at 8.2 δ (2 protons) which can be attributed only to an exocyclic amino group. Therefore, this strongly suggests that the predominant tautomeric form (10) of II in DMSO-d<sub>6</sub> is the "amino" form.

A recent study (11) has revealed that the coupling constants between the C<sub>1'</sub> and C<sub>2'</sub> protons of certain anomeric nucleosides were very similar and could not be used for anomeric assignment but utilization of the chemical shifts of the anomeric protons gave very useful and reproducible results. It was observed that the absorption peak for the anomeric proton of C<sub>1'</sub>, C<sub>2'</sub>-*cis* nucleosides appeared at a lower field than the corresponding anomeric proton of C<sub>1'</sub>, C<sub>2'</sub>-*trans* nucleoside. If II were the α anomer then the chemical shift for the anomeric proton should be the same as that observed for 3-β-D-ribofuranosyladenine, since the configuration around C<sub>1'</sub> and C<sub>2'</sub> would be identical. However, the absorption peak for the anomeric proton of II occurs at 6.6 δ (Fig. 2) while the absorption peak for the anomeric proton of 3-β-D-ribofuranosyladenine (12) occurs at 5.95 δ. This definite deshielding of the anomeric proton of II strongly suggests a C<sub>1'</sub>, C<sub>2'</sub>-*cis* nucleoside. This anomeric configuration should be expected since 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride has been previously shown (5, 13) to produce β-D-arabinofuranosides (C<sub>1'</sub>, C<sub>2'</sub>-*cis* nucleosides). Therefore, the anomeric configuration of II is assigned as β and the total structural assignment as 3-β-D-arabinofuranosyladenine (II).

#### EXPERIMENTAL (19)

##### 3-(2',3',5'-tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (I).

The crude 9-(2',3',5'-tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (117 g.) was recrystallized from warm 2-propanol as previously reported (5). The precipitate [9-(2',3',5'-tri-*O*-benzyl-β-D-arabino-

furanosyl)adenine, 68 g.] was collected by filtration and the filtrate concentrated *in vacuo* to one-tenth volume. The solid which formed on cooling (29.5 g., m.p. 122-140°) was removed by filtration and recrystallized twice from ethyl acetate to afford 8.4 g. of a white crystalline compound, m.p. 161-163°; [α]<sub>D</sub><sup>25</sup> +96.0° (C = 1.5, CH<sub>2</sub>Cl<sub>2</sub>).  
Anal. Calcd. for C<sub>31</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub>: C, 69.25; H, 5.81; N, 13.03. Found: C, 69.20; H, 5.70; N, 13.07.

##### 3-β-D-Arabinofuranosyladenine (II).

To a warm solution (50°) of 50% aqueous ethanol (325 ml.) containing I (2.0 g.) was added one g. of 10% palladium on carbon. The reaction mixture was then treated with hydrogen (50 p.s.i.) on a Parr shaker at 65° for 26 hours. The catalyst was removed from the hot solution by filtration through Celite and the filtrate concentrated to 75 ml. *in vacuo* and cooled overnight at 10°. The solid which had separated from the solution was collected by filtration to afford 0.10 g. of a crystalline compound, m.p. 202-205°, dec. This compound was characterized as a mono benzyl derivative of II by utilization of p.m.r. spectra (5 protons, 7.32 δ). The filtrate was evaporated to dryness *in vacuo* to afford 0.83 g. of solid material. This residue was triturated with 55 ml. of boiling ethanol (anhydrous) and allowed to cool to room temperature. The solid was removed by filtration from the cooled mixture to afford 0.45 g. of crude product. A small sample (0.10 g.) was recrystallized from methanol to furnish 0.05 g. of chromatographically pure product, m.p. 232-234°, dec; [α]<sub>D</sub><sup>25</sup> +68.5° (C = 0.4, H<sub>2</sub>O).  
Anal. Calcd. for C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>: C, 44.94; H, 4.91; N, 26.21. Found: C, 44.93; H, 5.05; N, 26.06.

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